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Quality information in spontaneous reports

One important function of pharmacovigilance or drug safety monitoring is to provide early warning signals of previously unknown adverse effects of medicines.<1> The World Health Organization (WHO) defines a signal as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously."<2>

Spontaneous reporting systems play a major role in the detection of new adverse drug reactions (ADRs). In fact, in most instances it is the only early signalling method available for newly marketed drugs and infrequently used drugs.<3> Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information.<2>

To ensure quality information for the assessment of individual ADRs, case reports should contain certain basic

information. To strengthen the ability to detect signals, specific criteria have been proposed<4> including the suggestion that ADR reports should contain the following essential items:

- Source of case (e.g., reporting physician, pharmacist)
- Case identification (patient's initials, chart number)
- Sex of patient
- Age of patient
- Description of reaction
- Name of drug, with brand name whenever possible
- Treatment dates
- Reaction onset date
- All concomitant drugs, with doses and dates
- Indication for treatment
- Underlying diagnosis
- Outcome

Additional information valuable in the assessment of the report includes: relevant medical history; response to dechallenge (stopping the drug); and response to rechallenge (restarting the drug).

All of these elements are found on Health Canada's ADR reporting form (available in the Compendium of Pharmaceuticals and Specialties).

When a potential signal is detected, various actions may occur. This may involve a search for similar cases in other databases such as the WHO database. The WHO Programme on International Drug Monitoring, in which Canada is a participating country, pools reports from over 50 countries in one database. This pooling of data enhances the ability to compare and identify trends in ADR profiles, and to identify rare, serious, unexpected reactions as early as possible. Other actions may include further monitoring, postmarketing studies, labelling changes, "Dear Health Professional" letters, dissemination of information through this newsletter or in medical journals, media alerts or, in rare situations, withdrawal of the drug from the market.

Signals are essentially suspicions. Assessment of all available data is required to improve rational decision-making in pharmacovigilance. Therefore, a good quality case report is important for the ongoing surveillance of drug safety.

This article is under the direction of: Amal Hélal, BSc Phm, Bureau of Drug Surveillance.

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Donepezil: suspected adverse reactions

Donepezil (Aricept®), a reversible cholinesterase inhibitor indicated for the symptomatic treatment of mild to moderate dementia of the Alzheimer's type, received its approval for marketing in August 1997. As of April 1998 the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) has received 43 Canadian reports associated with the use of donepezil, comprising 106 suspected reactions (67 expected and 39 not expected). Thirty-six reports were classified as serious and 7 as non-serious; 10 of the serious reports and 1 non-serious report did not mention concomitant drug use or medical conditions other than Alzheimer's disease. The 43 cases involved 25 women, 15 men and 3 people of unknown sex. The mean age was 74.5 (range 51 to 90) years.

Three of the patients died. One patient experienced a massive cerebrovascular accident 2 weeks after starting donepezil. In the second case, donepezil was stopped after one dose when the patient experienced extreme weakness and somnolence; 2 days later the patient died of unknown causes. In the third case, the patient experienced syncope while taking donepezil; the patient died of unknown causes within 2 months after donepezil was stopped. None of the 3 reports mentioned any history of other serious medical conditions, and 2 did not report use of concomitant drugs. The reports of reactions included the following: *cardiovascular:* arrhythmia (1), cerebrovascular disorder (5), cardiac fibrillation (1), heart block (1), myocardial infarction (1), edema (1), tachycardia (1) and thrombophlebitis (1); *gastrointestinal:* abdominal pain (1), hemorrhage (3), nausea (3) and vomiting (4); *neurologic:* convulsions (4), dizziness (1), dyskinesia (1), abnormal gait (1), headache (1), stupor (1) and tremor (1); *psychiatric:* aggressive reaction (1), anorexia (1), anxiety (2), confusion (2), delirium (1), delusion (1), manic reaction (1), schizophrenic reaction (1) and sleep disorder (4); *respiratory:* abnormal chest x-ray (1), cough (1), dyspnea (1), pneumonia (1), pulmonary congestion (2) and respiratory insufficiency (1); *other:* 31 reactions.

Donepezil is metabolized by the cytochrome P450 enzymes (CYP) 2D6 and 3A4. Currently only limited data are available regarding the effect of drugs or food on the drug's metabolism.<1> Theoretically, however, drugs that inhibit these 2 enzymes may increase the plasma level of donepezil. Eight reports described reactions associated with donepezil in which concomitant drugs were taken that inhibit CYP 2D6 or 3A4, including diltiazem, fluoxetine, paroxetine and sertraline. Most of the reported reactions are noted in the product monograph, and none is indicative of excessive plasma levels of donepezil.

Some of the 106 suspected adverse reactions may be associated with chronic illnesses common in elderly people, and certain reactions (e.g., seizures and confusion) may be manifestations of Alzheimer's disease itself. In addition, the gastrointestinal

reactions such as anorexia, nausea and vomiting are expected because of donepezil's cholinomimetic effects. However, data are limited on the use of donepezil in patients with renal or hepatic impairment and on its concomitant use with drugs that interact with CYP 2D6 and 3A4. Therefore, these patients should be monitored closely for adverse events. All adverse reactions should be reported because data collected through ongoing pharmacovigilance improves our knowledge of donepezil's safety profile.

This article is under the direction of: Pascale Springuel, BPharm, Bureau of Drug Surveillance.

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Olanzapine: hematological reactions

Olanzapine (Zyprexa®) is a new antipsychotic drug indicated for the acute and maintenance treatment of schizophrenia and related psychotic disorders. It is structurally similar to clozapine,<1> an antipsychotic drug approved for the management of treatment-resistant schizophrenia. Olanzapine has been found to improve both the positive (hallucinations, delusions, hostility) and negative (blunted affect, emotional and social withdrawal) symptoms of schizophrenia and has a lower propensity for causing extrapyramidal symptoms than does haloperidol.<2,3>

With clozapine, a major limitation of its use is the high incidence of agranulocytosis. This reaction has been reported to occur in about 1% of treated patients per year and has necessitated regular blood monitoring.<4> It has been postulated that a reactive metabolite is responsible for clozapine-induced agranulocytosis.<5> Although olanzapine has a similar structure that should oxidize to a reactive intermediate, no cases of agranulocytosis and no evidence of hemotoxicity were seen during the premarket clinical trials, which included approximately 2500 patients treated with olanzapine.<3,4>

Olanzapine received approval to be marketed in Canada in July 1996. As of April 1998 the CADRMP had received 6 reports of decreased hematological values associated with the use of olanzapine.

In the first case a 35-year-old man experienced a decreased granulocyte count with normal total white blood cell count (WBC) 1 1/2 months after starting olanzapine therapy. The physician also suspected a viral infection as a potential causative factor. Over 1 year earlier he had had a decreased WBC count during clozapine therapy. In the second case, a 75-year-old woman had a significant decrease in WBC count 3 days after starting olanzapine; the count returned to normal 1 day after olanzapine was stopped. Confounding

factors in this case included the use of concomitant drugs reported to rarely cause agranulocytosis and a history of breast cancer and lymphoma. The third case involved a 46-year-old man in whom pancytopenia developed. The report indicated that the reaction was due to a medical problem of megaloblastic anemia secondary to vitamin B_{12} and folate deficiency and not to the olanzapine. Olanzapine therapy was restarted in this patient, with no subsequent problems.

The remaining 3 cases involved men aged 34 to 66 years who had had a decreased WBC count with decreased granulocyte count (2 cases) or neutrophil count (1 case) during clozapine treatment. Although their hematological values were still low, each patient was switched to olanzapine.

In 2 cases olanzapine was started less than 1 week after stopping the clozapine. The olanzapine was stopped within 3 days because the WBC count continued to decrease. Two months later the WBC and granulocyte counts returned to normal. This recovery time contrasts with data from one study in which the mean time to recovery from clozapine-induced agranulocytosis (no exposure to olanzapine) was 3 days.<6> No confounding medical conditions were reported in these 2 cases.

In the third case the patient was switched to olanzapine within 3 weeks after receiving clozapine; he died after 2 weeks of olanzapine therapy. His WBC and neutrophil counts had increased after switching to the olanzapine. Three days before death the olanzapine dosage had been increased to 20 mg, and the day before death fever developed. Concomitant medications included methotrimeprazine (300 mg/d), and the addition of lithium (600 mg/d), lorazepam (2 mg/d) and chloral hydrate (2 g/d) the day before he died. The cause of death was reported as unknown.

Pre- and postmarketing experience has shown that olanzapine does not appear to be associated with a high incidence of agranulocytosis. However, certain authors have raised the possibility that, when acute granulocyte depression already exists, early institution of olanzapine may delay recovery.<6> However, this evidence is currently based on limited experience at one clinical site.

This article is under the direction of: Claire-Marie Wray, PhD and Ann Sztuke-Fournier, BPharm, Bureau of Drug Surveillance.

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COMMUNIQUÉ

The purpose of this section is to increase awareness of ADRs recently reported to the CADRMP. The following cases have been selected on the basis of their seriousness, or the fact that the reactions do not appear in the product monograph. They are intended to prompt reporting.

Valproic acid (Depakene®)
Three cases of pancreatitis occurring with the administration of valproic acid for the treatment of seizures were recently reported to the CADRMP. They involved 2 children (3-year-old boy and 14-year-old girl) and 1 patient of unknown age and sex. The adverse event was diagnosed 18 months after starting therapy in 1 patient and 9 months after in another patient, who was also taking sucralfate, cisapride, omeprazole and chloral hydrate. All 3 patients were admitted to hospital. At the time of reporting, 1 patient had not yet recovered;the outcomes of the other 2 were not provided.

Cefaclor (Ceclor®)
Noteworthy is the reported and published case of a 12-year-old girl in whom hypersensitivity myocarditis developed due to an allergic reaction to cefaclor given to treat otitis media ('*J Pediatr*' 1998;132:172-3). The patient was admitted to hospital with acute renal failure and a rash compatible with erythema multiforme 1 week after starting the antimicrobial therapy. Subsequently, she showed signs of low cardiac output. The report states that the patient had clinical and histologic features of hypersensitivity myocarditis. The child's condition dramatically improved within 48 hours after stopping the drug and starting corticosteroids and immunoglobulins.

Latanoprost (Xalatan™)
Latanoprost, a new prostaglandin, is indicated for the reduction of intraocular pressure in the treatment of glaucoma. Two reports of serious suspected cardiovascular reactions were received in 1997. One case involved a woman who experienced a racing heart and palpitations. She was not taking any concomitant drugs and had no

history of drug allergy. The second involved a 71-year-old man with a history of myocardial infarction and of "much greater than normal drug sensitivity." Within 20 minutes after instilling 1 drop of latanoprost diluted with distilled water to one-fifth its strength, he experienced headache and, 12 hours later, chest pain and bronchial constriction lasting for 10 hours. Mild chest discomfort then occurred for 24 hours. After the symptoms subsided latanoprost was resumed at one-twenty-fifth its strength, with no side effects.

Protease inhibitors – fat distribution

Four reports were received in 1998 describing reactions involving fat distribution associated with the use of protease inhibitors in the treatment of HIV infection: breast enlargement and abdominal distention (2), buffalo hump (1) and "Crix" belly (weight gain centred around the waist) (1). Three cases involved indinavir, and one involved saquinavir. The patients (2 women, 1 man, 1 sex unknown) ranged in age from 38 to 45 years. The time to onset of the reaction ranged from 7 to 10 months. Common concomitant medications for all 4 patients included stavudine (d4T) and lamivudine (3TC).

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If you have observed comparable cases or any other serious events, *please report* them to the Adverse Drug Reaction Reporting Unit, Continuing Assessment Division, Bureau of Drug Surveillance, AL 4103B1, Ottawa ON K1A 1B9, fax 613 957-0335; or to a participating regional centre.

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www.hc-sc.gc.ca/hpb-dgps/therapeut

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Please Note: A voluntary reporting system thrives on intuition, lateral thinking and openmindedness. For these reasons, most adverse drug reactions (ADRs) can be considered only to be suspicions, for which a proven causal association has not been established. Because there is gross undereporting of ADRs and because a definite causal association cannot be determined, this information cannot be used to estimate the incidence of adverse reactions.

ADRs are nevertheless invaluable as a source of potential new and undocumented signals.